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|   |  |  |   |
|---|--|--|---|
| <b>UTILITY<br/>PATENT APPLICATION<br/>TRANSMITTAL</b><br><small>(Only for new nonprovisional applications under 37 CFR 1.53(b))</small> |  | Attorney Docket No.                      | 660005.98757  |
|   |  | First Inventor or Application Identified | Michael C. Barney et al.  |
|   |  | Title                                    | Use of Hop Acids to Inhibit Growth of <i>S. aureus</i> and Prevent Toxic Shock Syndrome |
|   |  | Express Mail Label No.                   | EK290771473US   |

|  |  |
|--|--|
| <b>APPLICATION ELEMENTS</b><br><small>See MPEP Chapter 600 concerning utility patent application contents.</small> | <b>ADDRESS TO:</b><br>Assistant Commissioner for Patents<br>Box Patent Application<br>Washington, D.C. 20231 |
|--|--|

- 1 ☒ **Fee transmittal Form**  
(Submit an original and a duplicate for fee processing)
- 2 ☒ **Specification** (Total Pages 12)  
*(preferred arrangement set forth below)*
- Descriptive title of the invention
  - Cross References to Related Applications
  - Statement Regarding Fed Sponsored R&D
  - Background of the Invention
  - Brief Summary of the Invention
  - Detailed Description
  - Claim(s)
  - Abstract of the Disclosure

6. ☐ Microfiche Computer Program *(Appendix)*
7. Nucleotide and/or Amino Acid Sequence Submission  
*(if applicable, all necessary)*
- a. ☐ Computer readable Copy
  - b. ☐ Paper Copy
  - c. ☐ Statement Verifying identity of above

- 3 ☐ Drawing(s) (35 USC 113) (Total Sheets ☐)
4. Oath or Declaration (Total Pages ☐)
- a. ☒ Newly unexecuted (original or copy)
  - b. ☐ Copy from prior Application [37 CFR 1.63(d)]  
(for continuation/divisional with Box 17 completed)
- [Note Box 5 below]**
- i. ☐ **DELETION OF INVENTOR(S)**  
Signed Statement attached deleting inventor(s) named in prior application,

- 5 ☐ Incorporation By Reference (useable if Box 4b is checked)  
The entire disclosure of the prior application from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference herein.

|   |   |
|---|---|
| <b>ACCOMPANYING APPLICATION PARTS</b>   |   |
| 8 <input type="checkbox"/>  | Assignment Papers (cover sheet & documents)   |
| 9 <input type="checkbox"/>  | 37 CFR 3.73(b) Statement <input checked="" type="checkbox"/> Power of Attorney<br><small>(where there is an assignee)</small> |
| 10 <input type="checkbox"/>   | English Translation Document <i>(if applicable)</i>   |
| 11 <input checked="" type="checkbox"/>  | Information Disclosure Statement (IDS)/PTO-1449 <input checked="" type="checkbox"/> Copies of IDS Citations                   |
| 12 <input type="checkbox"/>   | Preliminary Amendment   |
| 13 <input checked="" type="checkbox"/>  | Return receipt postcard (MPEP 503)<br><i>(Should be specifically itemized)</i>  |
| 14 <input type="checkbox"/>   | * Small Entity Statement(s) <input type="checkbox"/> Statement filed in prior application<br>Status still proper and desired  |
| 15 <input type="checkbox"/>   | Certified copy of priority Document(s)<br><i>(if foreign priority is claimed)</i>   |
| 16 <input type="checkbox"/>   | Other:  |
| * A new statement is required to pay small entity fees, except where one has been filed in a prior application and is being relied upon |   |

17. If a **CONTINUING APPLICATION**, check appropriate box and supply the requisite information:
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- Prior application information: Examiner: \_\_\_\_\_ Group/Art Unit: \_\_\_\_\_

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| <small>(Insert Customer No. or Attach bar code label)</small> |                                     |  |              |
| NAME  | David M. Kettner<br>Quarles & Brady |  |              |
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|                   |                    |                                   |           |
|-------------------|--------------------|-----------------------------------|-----------|
| Name (Print/Type) | David M. Kettner   | Registration No. (Attorney/Agent) | 45,589    |
| Signature         | <i>[Signature]</i> | Date                              | 9-18-2000 |

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**FEE TRANSMITTAL**

Patent fees are subject to annual revision.

Small Entity payments must be supported by a small entity statement  
otherwise large entity fees must be paid. See Forms PTO/SB/09-12  
See 37 C.F.R. §§1.27 and 1.28

TOTAL AMOUNT OF

\$ 690.00

**Complete if Known**

Application Number

Filing Date

herewith

First Named Inventor

Michael C. Barney

Group Art Unit

Examiner Name

Attorney Docket Number

660005.98757

**METHOD OF PAYMENT (check one)**

- 1.
- ☒
- The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

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Quarles &amp; Brady LLP

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- Fee Required Under 37
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- CFR 1.16 and 1.17
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- 1.18 at the Mailing of the Notice of
- 
- Allowance, 37 CFR 1.311(b)

- 2.
- ☐
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**FEE CALCULATION (fees effective 11/10/98)****1. FILING FEE**

| Large Entity<br>Fee<br>Code | Large Entity<br>Fee<br>(\$) | Small Entity<br>Fee<br>Code | Small Entity<br>Fee<br>(\$) | Fee Description        | Fee Paid |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|------------------------|----------|
| 101                         | 690                         | 201                         | 345                         | Utility filing fee     | 690.00   |
| 106                         | 310                         | 206                         | 155                         | Design filing fee      |          |
| 107                         | 480                         | 207                         | 240                         | Plant filing fee       |          |
| 108                         | 690                         | 208                         | 345                         | Reissue filing fee     |          |
| 114                         | 150                         | 214                         | 75                          | Provisional filing fee |          |

SUBTOTAL (1) (\$) 690.00

**2. CLAIMS**

| Total Claims              | Extra    | Fee from<br>below | Fee Paid |
|---------------------------|----------|-------------------|----------|
| 14                        | -20**= 0 | X                 |          |
| Independent<br>Claims     | 3        | -3**= 0           | X        |
| Multiple Dependent Claims |          |                   |          |

\*\* or number previously paid, if greater, For reissues see below

| Large Entity<br>Fee<br>Code | Large Entity<br>Fee<br>(\$) | Small Entity<br>Fee<br>Code | Small Entity<br>Fee<br>(\$) | Fee Description  |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|--|
| 103                         | 18                          | 203                         | 09                          | Claims in excess of 20                                       |
| 102                         | 78                          | 202                         | 39                          | Independent claims in excess of 3                            |
| 104                         | 260                         | 204                         | 130                         | Multiple dependent claim                                     |
| 109                         | 78                          | 209                         | 39                          | **Reissue independent claims<br>over original patent         |
| 110                         | 18                          | 210                         | 09                          | **Reissue claims in excess of 20<br>and over original patent |

SUBTOTAL (2) (\$)

**FEE CALCULATION (continued)****3. ADDITIONAL FEES**

| Large Entity<br>Fee<br>Code | Large Entity<br>Fee<br>(\$) | Small Entity<br>Fee<br>Code | Small Entity<br>Fee<br>(\$) | Fee   |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|---|
| 105                         | 130                         | 205                         | 65                          | Surcharge - late filing fee or oath   |
| 127                         | 50                          | 227                         | 25                          | Surcharge - late provisional filing fee or<br>cover sheet                     |
| 139                         | 130                         | 139                         | 130                         | Non-English specification   |
| 147                         | 2,520                       | 147                         | 2,520                       | For filing a request for reexamination  |
| 112                         | '920                        | 112                         | '920                        | Requesting publication of SIR prior to<br>Examiner action                     |
| 113                         | '1,840                      | 113                         | '1,840                      | Requesting publication of SIR after Examiner<br>action                        |
| 115                         | 110                         | 215                         | 55                          | Extension for reply within first month  |
| 116                         | 380                         | 216                         | 190                         | Extension for reply within second month                                       |
| 117                         | 870                         | 217                         | 435                         | Extension for reply within third month  |
| 118                         | 1,360                       | 218                         | 680                         | Extension for reply within fourth month                                       |
| 128                         | 1,850                       | 228                         | 925                         | Extension for reply within fifth month  |
| 119                         | 300                         | 219                         | 150                         | Notice of Appeal  |
| 120                         | 300                         | 220                         | 150                         | Filing a brief in support of an appeal  |
| 121                         | 260                         | 221                         | 130                         | Request for oral hearing  |
| 138                         | 1,510                       | 138                         | 1,510                       | Petition to institute a public use proceeding                                 |
| 140                         | 110                         | 240                         | 55                          | Petition to revive unavoidsably abandoned<br>application                      |
| 141                         | 1,210                       | 241                         | 605                         | Petition to revive unintentionally abandoned<br>application                   |
| 142                         | 1,210                       | 242                         | 605                         | Utility issue fee (or reissue)  |
| 143                         | 430                         | 243                         | 215                         | Design issue fee  |
| 144                         | 580                         | 244                         | 290                         | Plant issue fee   |
| 122                         | 130                         | 122                         | 130                         | Petitions to the Commissioner   |
| 123                         | 50                          | 123                         | 50                          | Petitions related to provisional applications                                 |
| 126                         | 240                         | 126                         | 240                         | Submission of Information Disclosure Stmt                                     |
| 581                         | 40                          | 581                         | 40                          | Recording each patent assignment per<br>property (times number of properties) |
| 146                         | 690                         | 246                         | 345                         | Filing a submission after final rejection<br>(37 CFR 1.129(a))                |
| 149                         | 690                         | 249                         | 345                         | For each additional invention to be examined<br>(37 CFR 1.129(b))             |

Other fee (specify)

Other fee (specify)

SUBTOTAL (3) (\$)

\* Reduced by Basic Filing Fee Paid

**SUBMITTED BY**Typed or  
Printed Name

David M. Kettner

Registration No.  
(Attorney/Agent)

45,589

Signature

Date

September 12, 2000

**Complete (if applicable)**

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September 18, 2000

Commissioner of Patents  
Box Patent Application  
Washington DC 20231

Re: Filing New Patent Application

Dear Sir:

Enclosed for filing please find a new patent application  
entitled: USE OF HOP ACIDS TO INHIBIT THE GROWTH OF STAPHYLOCOCCUS  
AUREUS AND PREVENT TOXIC SHOCK SYNDROME

by Michael C. Barney  
Alfonso L. Navarro  
David S. Ryder

The undersigned hereby certifies that this document is being  
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Respectfully submitted,

USE OF HOP ACIDS TO INHIBIT  
GROWTH OF STAPHYLOCOCCUS AUREUS AND  
PREVENT TOXIC SHOCK SYNDROME

5 CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority from provisional patent application Serial No. 60/158,810, filed October 12, 1999.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH  
OR DEVELOPMENT

10 Not applicable.

BACKGROUND OF THE INVENTION

The present invention relates to the use of compounds to affect the growth of certain bacterial species. More specifically, the present invention relates to the use of  
15 tetrahydroiso alpha acids or hexahydro beta acids at concentrations effective to kill, inhibit, or otherwise control the growth or proliferation of *Staphylococcus aureus* without preventing the growth of *Lactobacillus*. The inhibition of *S. aureus* in accordance with the present invention thus provides useful products, compositions and methods for treating the diseases associated with *S. aureus* infections and infestations,  
20 i.e., toxic shock syndrome, without disrupting the normal bacterial flora in the area of its application.

A commonly known disease caused by *S. aureus* is toxic shock syndrome (TSS). TSS is a severe, toxin-induced disease arising from the exposure to the *S. aureus* toxin called toxic shock syndrome toxin-1 (TSST-1) (Iandolo, Ann. Rev. of Micro. 43:275-  
25 402, 1989). The disease is characterized by a sudden onset of symptoms, including high fever, chills, rash, vomiting or diarrhea, and a rapid drop in blood pressure leading to shock.

Toxic shock syndrome has been reported to occur in both men and women of all ages, with approximately two cases occurring annually per 10,000 people. TSS,  
30 however, is most commonly seen in menstruating women in whom the primary site of infection is the vagina. Epidemiological evidence especially suggests that women who

use highly absorbent tampons incur an increased risk for developing the disease as the highly absorbent tampon serves as a suitable environment for *S. aureus* growth. TSS has also been reported to occur in infants, children, men, and non-menstruating women, but at a lower frequency. These cases are generally not associated with the use of  
5 tampons, but result from skin wounds or infections in other parts of the body. The use of barrier contraceptives has also been implicated as another risk factor.

Because of the sudden onset of the disease, persons suffering from TSS may not receive appropriate medical intervention before serious complications result. Such complications may include kidney failure, heart failure, liver failure and profound  
10 shock. Accordingly, there is a very strong emphasis on disease prevention. For example, women are cautioned against using high absorbency tampons. However, many women are not willing to sacrifice the comfort and convenience of using high absorbency tampons for what they perceive to be a remote risk of developing TSS. Therefore, considerable effort has been directed toward developing new tampons  
15 capable of reducing the risk of contracting TSS as compared to conventional tampons.

Various approaches for preventing toxic shock syndrome from tampon use have been advanced. One such method includes incorporating bactericidal or bacteriostatic agents (i.e., antibiotics or phenol) into the tampon to inhibit *S. aureus* growth. Other methods include the incorporation of agents which prevent the production of TSST-1 or  
20 inactivate TSST-1. For example, U.S. Patent 4,405,323 discloses the incorporation of an antibacterial agent, such as povidone-iodine, mercury, zinc, penicillin, erythromycin, and nitrofurazone, within a tampon to prevent TSS. U.S. Patent 4,431,427 discloses the incorporation of a water-soluble acid (i.e., citric, glycolic, malic, tartaric, or lactic acid) in a tampon at an amount sufficient to maintain a pH of 4.5 or less in the fluids absorbed  
25 by the tampon so as to inhibit the growth of pathogenic bacteria. PCT publication WO 86/05388 discloses that the inclusion of a nontoxic divalent cation, such as magnesium, barium, calcium, strontium, or the like, in an absorptive pad has the effect of inhibiting the production of TSST-1 by *S. aureus*. U.S. Patent 4,585,792 discloses that L-ascorbic acid may be delivered on a tampon to the vaginal area so as to inactivate the toxins  
30 associated with TSS. U.S. Patent 5,389,374 discloses that the production of *S. aureus* enterotoxins can be inhibited by exposing the bacterium to an absorbent material treated with either a mono- or diester of apolyhydric aliphatic alcohol.

Although the use of some of these approaches have proven effective in inhibiting the growth of *S. aureus* and TSS, their use may also be problematic. For example,  
35 exposing a bacterial population to antibiotics may select for antibiotic resistant mutants, and decrease the efficacy of the antibiotic in treating future infections. In addition, the inclusion of conventional antibiotics will likely result in a considerable increase in cost

to the consumer. Moreover, the use of antibiotics or other bactericidal or bacteriostatic agents may have the undesirable effect of disrupting the normal bacterial flora present in their area of application, ultimately resulting in the onset of other bacterial infections and diseases. For example, *Lactobacillus* is one of the predominant bacteria among  
5 normal vaginal flora. The administration of a compound which inhibits *Lactobacillus* may also have the added affect of promoting the establishment of other, less desirable microorganisms which are also present in the vagina. For instance, a low number of *Candida albicans* may be present in the vagina of many healthy asymptomatic women. The administration of a compound which inhibits the growth of *Lactobacillus* may also  
10 have the added affect of allowing *C. albicans* to grow and predominate, resulting in a yeast infection.

It would be advantageous, therefore, to have a method for preventing TSS which does not affect normal bacterial flora, and does not allow for the selection of antibiotic resistant bacteria, and does not result in a substantial increase in the overall cost to the  
15 consumer. In particular, what is needed is a relatively inexpensive method for inhibiting the growth of *S. aureus* without preventing the growth of *Lactobacillus* or other normal microflora.

#### BRIEF SUMMARY OF THE INVENTION

20 The present invention is summarized in that certain compounds are disclosed which are capable of affecting the growth of *Staphylococcus aureus* without preventing the growth of *Lactobacillus* when applied in certain concentrations. These compounds are selected from the group consisting of tetrahydroiso alpha acids, hexahydro beta acids, and salts, mixtures or combinations thereof, and are applied in an amount  
25 effective to kill, inhibit, or otherwise control the growth or proliferation of *S. aureus* without preventing the growth of *Lactobacillus*. An effective amount of such compounds, for example, includes a concentration in the range of from about 0.2 ppm to about 25 ppm, or more preferably in the range of from about 0.5 ppm to about 12.5 ppm.

In addition, the present invention includes a product comprising an absorbent  
30 material and a compound selected from the group consisting of tetrahydroiso alpha acids, hexahydro beta acids, salts thereof, and mixtures thereof, in an amount effective to kill, inhibit, or otherwise control the growth or proliferation of *S. aureus* without preventing the growth of *Lactobacillus*. The material may include, for example, cellulosic fiber material such as those typically used in feminine hygiene products (i.e.,  
35 feminine napkins, tampons, etc.), or used to absorb bodily fluids or apply compounds employed in preventing or treating bacterial infections.

The present invention also includes a composition comprising a pharmaceutically acceptable carrier, and a compound selected from the group consisting of tetrahydroiso alpha acids, hexahydro beta acids, salts thereof, and mixtures thereof, in an amount effective to kill, inhibit, or otherwise control the growth or proliferation of *S. aureus* without preventing the growth of *Lactobacillus*. The carrier may include, for example, topical ointments or washes formulated to facilitate effective administration of the compound.

It is an object of the present invention to provide a compound having inhibitory activity against *S. aureus* and minimal to no inhibitory activity against *Lactobacillus* when applied at certain concentrations.

It is also an object of the present invention to provide products and compositions for contacting *S. aureus* with such a compound.

It is yet another object of the invention to provide a method for preventing or treating *S. aureus* infection or infestation.

Other objects, advantages and features of the present invention will become apparent from the following detailed description and examples.

#### BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Not applicable.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention discloses compounds which, when applied at certain concentrations, affect the growth of *Staphylococcus aureus* without preventing the growth of *Lactobacillus*. The compounds are selected from the group consisting of tetrahydroiso alpha acids, hexahydro beta acids, salts thereof, and mixtures thereof, and may be combined with various materials or carriers to form products and compositions suitable for facilitating effective administration. The present invention also discloses methods for using the compounds to prevent or treat *S. aureus* infection or infestation without disrupting the normal flora of *Lactobacillus* in its area of application.

We have discovered that the hop acids tetrahydroiso alpha and hexahydro beta have unexpectedly different bacteriocidal or bacteriostatic effects against *Lactobacillus* as compared to *S. aureus*. Specifically, *Lactobacillus* and *S. aureus* exhibit a differing level of sensitivity to tetrahydroiso alpha and hexahydro beta acids, with *S. aureus* being more sensitive than *Lactobacillus*. As a result, it is now possible to selectively inhibit *S. aureus* without preventing the growth of *Lactobacillus* by contacting the *S. aureus* with an amount of tetrahydroiso alpha acid or hexahydro beta acid which effectively inhibits *S. aureus* while allowing *Lactobacillus* to continue to grow.

The primary embodiment of the present invention is to provide a method for inhibiting *S. aureus* infection or infestation by contacting the *S. aureus* environment with an effective concentration of a compound which kills, inhibits, or otherwise controls the growth or proliferation of *S. aureus* without preventing the growth of

5 *Lactobacillus*. In the preferred embodiment, the *S. aureus* environment is exposed to an effective concentration of the compound in a range of from about 0.2 ppm to about 25 ppm, and more preferably, in a range of from about 0.5 ppm to about 12.5 ppm.

As used herein, the term "compound" is intended to include hexahydro beta acids, hexahydro beta salts, tetrahydroiso alpha acids, tetrahydroiso alpha salts, and

10 mixtures or combinations thereof.

To affect the growth of *S. aureus*, the compound may be placed in contact with a *S. aureus* environment either independently or as part of a composition or product wherein the composition or product contains an effective amount of the compound in accordance with the present invention. In another embodiment, the compound may be

15 layered or coated onto a barrier type contraceptive such as a diaphragm or contraceptive sponge that is placed in the *S. aureus* environment. The *S. aureus* environment may include, for example, any environment having a population of the *S. aureus* bacterium or an environment capable of allowing *S. aureus* to grow and proliferate. For instance, the environment may include, without limitation, wounds, lesions, tampons, the vagina,

20 sanitary napkins, gauze, diapers, suppositories, or any other possible areas susceptible to *S. aureus* infection or infestation.

As used herein, the term "product" includes those products capable of, either inherently or by virtue of the manner in which they are assembled, absorbing liquids such as water, urine, menstrual fluids, blood, wound exudates and the like. Such

25 products include, for example, catemenial products (e.g. tampons), wound dressings, suppositories, disposable diapers, and sanitary napkins, in addition to other kinds of tampons intended for medical, surgical, dental and/or nasal use. Products according to the present invention may be prepared according to known methods for manufacturing such products. In general, the products should be prepared to allow an effective amount

30 of the compound utilized to be placed in contact with the *S. aureus* environment.

In one embodiment, the product comprises of an absorbent material and an amount of compound which effectively kills, inhibits, or otherwise controls the growth or proliferation of *S. aureus* without preventing the growth of *Lactobacillus* when said product is exposed to the *S. aureus* environment. A used herein, the term "absorbent

35 material" includes, without limitation, natural fibers or synthetic fibers, films, foams, wood, pulp, peat moss, superabsorbent polymers and the like which are capable of, either inherently or by virtue of the manner in which they are assembled, absorbing



liquids such as water, urine, menstrual fluids, blood, wound exudates and the like.

The term "composition" includes those compositions capable of, either inherently or by virtue of their formulation, use as a topical ointment or wash applied to a wound, infection, or the like. Compositions may be formulated according to known methods for preparing pharmaceutically useful compositions. Formulations are described in detail in a number of sources which are well known and readily available to those skilled in the art. For example, *Remington's Pharmaceutical Science*, by E.W. Martin describes formulations which can be used in connection with the subject invention. In general, the compositions should be formulated such that an effective amount of the compound utilized is combined with the suitable carrier in order to facilitate effective administration.

In one embodiment, the composition consists of a douche for killing, inhibiting, or otherwise controlling the growth or proliferation of *S. aureus* in the vagina. This is particularly useful for providing a treatment to a woman to help fight against *S. aureus* infection or infestation that can cause toxic shock syndrome. Alternatively, the composition may be formulated as a topical ointment or wash for application to wounds or infections in other parts of the body.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof are to be included within the spirit and purview of this application and the scope of the appended claims. Following are examples which are intended to be purely illustrative, and should not be construed as limiting but merely exemplary.

## EXAMPLES

Minimal inhibitory concentration (MIC) assays of several hop compounds were conducted using a *Staphylococcus aureus* species and vaginal isolates *Lactobacillus vaginalias*, *Lactobacillus crispatus*, *Lactobacillus gasseri*, and *Lactobacillus jensenii* as test microorganisms. *Lactobacillus* assays were conducted in *Lactobacillus* MRS broth (Difco) tubes. A 0.1 ml aliquot of a 1% (w/w) solution of each hop acid in alcohol was added to a tube of sterile MRS broth to give a final concentration of 100 ppm of the hop. This solution was serially diluted in tubes with sterile MRS broth using a two-fold dilution series. A second dilution series prepared as above, but using 0.1 ml alcohol without hop acid, was used as a positive control of bacterial growth. Each tube was inoculated with a fresh culture ( $10^4$  cells) of a *Lactobacillus* species in MRS broth. The cultures were incubated anaerobically in a CO<sub>2</sub> incubator at 28°C for five days. Growth was evaluated by visually assessing and scoring development of turbidity in the tube of

broth.

The MIC assays for *Staphylococcus aureus* were conducted in Difco trypticase soy broth (TSB) using the same serial dilution technique and the inoculum level as described above. The pH of the TSB was adjusted to pH 7.0, pH 6.0, or pH 5.0 using hydrochloric acid. The tubes were incubated aerobically at 37°C for three days and growth was evaluated by visually assessing and scored the development of turbidity in the broth.

The results of MIC assay of tetrahydroiso alpha acids and hexahydro beta acids on *S. aureus* and *Lactobacillus* are shown in Tables 1 and 2, respectively. As illustrated by a comparison of Tables 1 and 2, it is evident that *S. aureus* is much more sensitive to tetrahydroiso alpha acids and hexahydro beta acids than the *Lactobacillus* species tested.

In particular, *Lactobacillus* exhibited strong growth in concentrations of hexahydro beta acid and tetrahydroiso alpha acid as high as 12.5 ppm. In contrast, *S. aureus* showed no to very weak growth in tetrahydroiso alpha acid or hexahydro beta acid concentrations as low as 1.56 ppm. The sensitivity of *S. aureus* also appeared to increase under acidic conditions, with the minimum inhibitory concentration decreasing to 0.78 ppm at pH 6.0 and to less than 0.2 ppm at pH 5.0. Normally, the pH of the vagina is in the range of about 4.5 to 5.0.

Table 1

| MIC Assays of Tetrahydroiso Alpha Acids and Hexahydro Beta Acids using <i>Staphylococcus aureus</i> |               |            |               |            |               |            |
|---|---------------|------------|---------------|------------|---------------|------------|
|   | TSB at pH 7.0 |            | TSB at pH 6.0 |            | TSB at pH 5.0 |            |
| Concentration (ppm)   | Tetra         | Hexa       | Tetra         | Hexa       | Tetra         | Hexa       |
| 100   | No growth     | No growth  | No growth     | No growth  | No growth     | No growth  |
| 50  | No growth     | No growth  | No growth     | No growth  | No growth     | No growth  |
| 25  | No growth     | No growth  | No growth     | No growth  | No growth     | No growth  |
| 12.5  | No growth     | No growth  | No growth     | No growth  | No growth     | No growth  |
| 6.25  | No growth     | No growth  | No growth     | No growth  | No growth     | No growth  |
| 3.125   | No growth     | No growth  | No growth     | No growth  | No growth     | No growth  |
| 1.56  | +/- Growth    | +/- Growth | No growth     | No growth  | No growth     | No growth  |
| 0.78  | + Growth      | + Growth   | No growth     | No growth  | No growth     | No growth  |
| 0.39  | ++ Growth     | ++ Growth  | +/- Growth    | No growth  | No growth     | No growth  |
| 0.2   | +++ Growth    | +++ Growth | ++ Growth     | + Growth   | No growth     | No growth  |
| 0   | +++ Growth    | +++ Growth | +++ Growth    | +++ Growth | +++ Growth    | +++ Growth |

Table 2.

| MIC Assays of Tetrahydroiso Alpha Acids and Hexahydro Beta Acids using<br><i>Lactobacillus</i> species |       |               |            |
|--|-------|---------------|------------|
|  |       | MRS at pH 6.3 |            |
| Concentration (ppm)  |       | Tetra         | Hexa       |
| 5  | 100   | No growth     | No growth  |
|  | 50    | No growth     | No growth  |
|  | 25    | +/- Growth    | +/- Growth |
|  | 12.5  | ++ Growth     | +++ Growth |
|  | 6.25  | +++ Growth    | +++ Growth |
| 10   | 3.125 | +++ Growth    | +++ Growth |
|  | 1.56  | +++ Growth    | +++ Growth |
|  | 0.78  | +++ Growth    | +++ Growth |
|  | 0.39  | +++ Growth    | +++ Growth |
|  | 0.2   | +++ Growth    | +++ Growth |
| 15   | 0     | +++ Growth    | +++ Growth |

## CLAIMS

### WE CLAIM:

1. A method for affecting the growth of *Staphylococcus aureus*, said method comprising the step of:
  - 5 contacting an environment containing *S. aureus* with a compound selected from the group consisting of hexahydro beta acids, hexahydro beta salts, tetrahydroiso alpha acids, tetrahydroiso alpha salts, mixtures thereof, and combinations thereof, in an amount effective to kill, inhibit, or otherwise control the growth or proliferation of *S. aureus* without preventing the growth of *Lactobacillus*.
  - 10 2. The method of claim 1, wherein the concentration of the compound is in the range of from about 0.2 ppm to about 25 ppm.
  3. The method of claim 1, wherein the compound is placed in contact with the *S. aureus* environment using a product comprising of an absorbent material and the compound.
  - 15 4. The method of claim 3, wherein the absorbent material is selected from the group consisting of a natural fiber, a synthetic fiber, a film, a foam, a wood, a pulp, a peat moss, and a superabsorbent polymer.
  5. The method of claim 3, wherein the product is selected from the group consisting of a tampon, wound dressing, suppository, disposable diaper, and sanitary  
20 napkin.
  6. The method of claim 1, wherein the compound is placed in contact with the *S. aureus* environment using a composition comprising of a pharmaceutically acceptable carrier and the compound.
  7. The method of claim 6, wherein the compound is either a douche or a  
25 topical ointment.
  8. The method of claim 1, wherein the compound is placed in contact with the *S. aureus* environment using a barrier contraceptive.

9. A composition comprising a pharmaceutically acceptable carrier, and a compound selected from the group consisting of hexahydro beta acids, hexahydro beta salts, tetrahydroiso alpha acids, tetrahydroiso alpha salts, mixtures thereof, and combinations thereof, in an amount effective to kill, inhibit, or otherwise control the growth or proliferation of *S. aureus* without preventing the growth of *Lactobacillus*.

10. The composition of claim 9, wherein the concentration of the compound is in the range of from about 0.2 ppm to about 25 ppm.

11. The composition of claim 9, wherein the pharmaceutically acceptable carrier is either a douche or a topical ointment.

10 12. A product comprising an absorbent material, and a compound selected from the group consisting of hexahydro beta acids, hexahydro beta salts, tetrahydroiso alpha acids, tetrahydroiso alpha salts, mixtures thereof, and combinations thereof, in an amount effective to kill, inhibit, or otherwise control the growth or proliferation of *S. aureus* without preventing the growth of *Lactobacillus*.

15 13. The product of claim 12, wherein the concentration of the compound is in the range of from about 0.2 ppm to about 25 ppm.

14. The product of claim 12, wherein the absorbent material is selected from the group consisting of a natural fiber, a synthetic fiber, a film, a foam, a wood, a pulp, a peat moss, and a superabsorbent polymer.

## ABSTRACT OF THE DISCLOSURE

The present invention provides methods, products, and compositions for selectively inhibiting the growth of *Staphylococcus aureus* without preventing the growth of *Lactobacillus* species. Specifically, the present invention discloses the use of tetrahydroiso alpha acid or hexahydro beta acid at a concentration effective to inhibit the growth of *S. aureus* without preventing the growth of *Lactobacillus*. The inhibition of *S. aureus* in accordance with the present invention thus provides useful methods, compositions and products such as feminine hygiene products for treating the diseases associated with *S. aureus* infections and infestations, i.e., toxic shock syndrome, without disrupting the normal bacterial flora in the area of its application.

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## SEQUENCE LISTING

Not applicable.

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|   |   |   |                               |                          |
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| <b>0010/PTO</b><br>Rev. 6/95  | <b>U.S. Department of Commerce</b><br>Patent and Trademark Office | <b>DECLARATION FOR</b>  | <b>Attorney Docket Number</b> | <b>660005.98757</b>      |
|   |   | <b>UTILITY OR DESIGN</b>  | <b>First Named Inventor</b>   | <b>Michael C. Barney</b> |
|   |   | <b>PATENT APPLICATION</b>   | <b>COMPLETE IF KNOWN</b>      |                          |
|   |   | <b>Application Number</b>   |                               |                          |
|   |   | <b>Filing Date</b>  | <b>Herewith</b>               |                          |
|   |   | <b>Group Art Unit</b>   |                               |                          |
| <input checked="" type="checkbox"/> Declaration Submitted with Initial Filing | OR  | <input type="checkbox"/> Declaration Submitted after Initial Filing | <b>Examiner Name</b>          |                          |

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**USE OF HOP ACIDS TO INHIBIT GROWTH OF STAPHYLOCOCCUS AUREUS AND PREVENT TOXIC SHOCK SYNDROME**

(Title of the Invention)

the specification of which

☒ is attached hereto

OR

☐ was filed on (MM/DD/YY)

as United States Application Number or PCT International

Application Number

and was amended on (MM/DD/YY)

(if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

| Prior Foreign Application Number(s) | Country | Foreign Filing Date (MM/DD/YY) | Priority Not Claimed     | Certified YES            | Copy Attached? NO        |
|-------------------------------------|---------|--------------------------------|--------------------------|--------------------------|--------------------------|
|                                     |         |                                | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
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☐ Additional foreign applications numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

| Application Number(s) | Filing Date (MM/DD/YY) | <input type="checkbox"/> Additional provisional |
|-----------------------|------------------------|---|
| 60/158,810            | 10/12/99               |   |



**DECLARATION**

Page 2

I hereby claim benefit under Title 35, United States Code §120 of any United States application(s), or §365(C) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application or PCT international application in the manner provided in the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

| U.S. Parent Application Number | PCT Parent Number | Parent Filing Date (MM/DD/YY) | Parent Patent Number (if applicable) |
|--------------------------------|-------------------|-------------------------------|--------------------------------------|
|                                |                   |                               |                                      |

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and all continuation and divisional applications based thereon, and to transact all business in the Patent and Trademark Office connected therewith:

☐ Firm Name  Customer Number or label   
OR  
☒ List attorney(s) and/or agent(s) name and registration number below

| Name                | Registration Number | Name                 | Registration Number |
|---------------------|---------------------|----------------------|---------------------|
| Thad F. Kryshak     | 19,428              | Gregory A. Nelson    | 30,577              |
| Neil Hamilton       | 19,869              | Keith M. Baxter      | 31,233              |
| Thomas W. Ehrmann   | 20,374              | John D. Franzini     | 31,356              |
| Barry E. Sammons    | 25,608              | Joseph W. Bain       | 34,290              |
| J. Rodman Steele    | 25,931              | Robert J. Sacco      | 35,667              |
| Nicholas J. Seay    | 27,386              | Jean C. Baker        | 35,433              |
| George E. Haas      | 27,642              | David G. Ryser       | 35,407              |
| Michael J. McGovern | 28,326              | Bennett J. Berson    | 37,094              |
| Carl R. Schwartz    | 29,437              | Michael A. Jaskolski | 37,551              |
|                     |                     | David M. Kettner     | 45,589              |

☐ Additional attorney(s) and/or agents named on a supplemental priority sheet attached hereto

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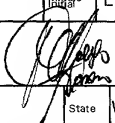
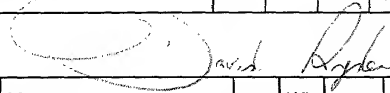
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Name of Sole or First Inventor:

A petition has been filed for this unsigned inventor

|   |                          |                |    |             |            |                   |           |
|---|--------------------------|----------------|----|-------------|------------|-------------------|-----------|
| Given Name  | Michael                  | Middle Initial | C. | Family Name | Barney     | Suffix, e.g., Jr. |           |
| Inventor's Signature  | <i>Michael C. Barney</i> |                |    |             |            | Date              | 9/8/2000  |
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| Additional inventors are being named on supplemental sheet(s) attached hereto |                          |                |    |             |            |                   | Applicant |

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| DECLARATION   |   |  |  |                |    |  |             |         |  | ADDITIONAL INVENTOR(S)<br>Supplemental Sheet         |                   |        |  |                     |  |  |
|---|---|--|--|----------------|----|--|-------------|---------|--|--|-------------------|--------|--|---------------------|--|--|
| Name of Additional Joint Inventor, if any:                                    |   |  |  |                |    |  |             |         |  | A petition has been filed for this unsigned inventor |                   |        |  |                     |  |  |
| Given Name  | Alfonso   |  |  | Middle Initial | L. |  | Family Name | Navarro |  |  | Suffix, e.g., Jr. |        |  |                     |  |  |
| Inventor's Signature  |  |  |  |                |    |  |             |         |  |  | Date              | 9/8/00 |  |                     |  |  |
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| City  | Milwaukee   |  |  | State          | WI |  | Zip         | 53202   |  |  | Country           | US     |  | Applicant Authority |  |  |
| Name of Additional Joint Inventor, if any:                                    |   |  |  |                |    |  |             |         |  | A petition has been filed for this unsigned inventor |                   |        |  |                     |  |  |
| Given Name  | David   |  |  | Middle Initial | S. |  | Family Name | Ryder   |  |  | Suffix, e.g., Jr. |        |  |                     |  |  |
| Inventor's Signature  |  |  |  |                |    |  |             |         |  |  | Date              | 9-8-00 |  |                     |  |  |
| Residence: City   | Mequon  |  |  | State          | WI |  | Country     | US      |  |  | Citizenship       | US     |  |                     |  |  |
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| Post Office Address   |   |  |  |                |    |  |             |         |  |  |                   |        |  |                     |  |  |
| City  | Mequon  |  |  | State          | WI |  | Zip         | 53092   |  |  | Country           | US     |  | Applicant Authority |  |  |
| Name of Additional Joint Inventor, if any:                                    |   |  |  |                |    |  |             |         |  | A petition has been filed for this unsigned inventor |                   |        |  |                     |  |  |
| Given Name  |   |  |  | Middle Initial |    |  | Family Name |         |  |  | Suffix, e.g., Jr. |        |  |                     |  |  |
| Inventor's Signature  |   |  |  |                |    |  |             |         |  |  | Date              |        |  |                     |  |  |
| Residence: City   |   |  |  | State          |    |  | Country     |         |  |  | Citizenship       |        |  |                     |  |  |
| Post Office Address   |   |  |  |                |    |  |             |         |  |  |                   |        |  |                     |  |  |
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| Name of Additional Joint Inventor, if any:                                    |   |  |  |                |    |  |             |         |  | A petition has been filed for this unsigned inventor |                   |        |  |                     |  |  |
| Given Name  |   |  |  | Middle Initial |    |  | Family Name |         |  |  | Suffix, e.g., Jr. |        |  |                     |  |  |
| Inventor's Signature  |   |  |  |                |    |  |             |         |  |  | Date              |        |  |                     |  |  |
| Residence: City   |   |  |  | State          |    |  | Country     |         |  |  | Citizenship       |        |  |                     |  |  |
| Post Office Address   |   |  |  |                |    |  |             |         |  |  |                   |        |  |                     |  |  |
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| Additional inventors are being named on supplemental sheet(s) attached hereto |   |  |  |                |    |  |             |         |  |  |                   |        |  |                     |  |  |